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Sleep Disorders

CASE 1

A 25-year-old woman complained of an 8-month history of excessive daytime somnolence. She stated that she had to take multiple naps during the day and had vivid dreams on falling asleep. Her friend had witnessed loss of muscle control in her legs following a significant change in emotional state such as anger or laughter. She had also experienced episodes of being paralyzed on awakening. Neurological examination was normal.

Localization

Excessive daytime somnolence (EDS) implies poor nocturnal sleep, which could be secondary to difficulty initiating or maintaining sleep. Dysfunctional sleep is nonlocalizing, and may implicate dysfunction in sleep or alerting centers in the hypothalamus, thalamus, or brainstem. Vivid dreams could be normal or represent visual hallucinations. Visual hallucinations may localize to the bilateral occipital cortex (elementary figures) or temporo-occipital junction (well-formed figures). Sudden lower extremity atonia may localize to the bilateral mesial frontal lobes, subcortical white matter, cerebral peduncles, basis pontis, pyramidal tracts, or corticospinal tracts in the spinal cord. Transient quadriparesis suggests bilateral upper or LMN dysfunction. There are no features in the history that suggest one over the other. In summary, the underlying process most likely involves the bilateral cerebral cortex, diencephalon, and brainstem.

Differential Diagnosis

The most likely diagnosis for a sleep disorder with EDS, hypnagogic hallucinations, cataplexy, and sleep paralysis is *narcolepsy*. This is rapid eye movement (REM)-sleep disorder associated with dysfunction in orexin (hypocretin)-secreting cells in the hypothalamus, and may be linked to human leukocyte antigen (HLA) DQB1*0602 on chromosome 6 in all ethnic groups. In 60–100% of cases, cataplexy occurs with EDS only. Sleep paralysis may

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occur in 25–50% of cases and the classic tetrad (as in this case) occurs in approximately 10% of patients. Other differentials that should be considered could be divided based on symptoms.

Differentials for EDS include *obstructive sleep apnea* (OSA), *sleep deprivation, drug-induced hypersomnolence* (alcohol, sedative-hypnotics, antihistamines, etc.), *medical causes* (chronic obstructive pulmonary disease [COPD], CHF, peptic ulcer disease, sleeping sickness), *neurological causes* (stroke, headache, painful peripheral neuropathies, fatal familial insomnia, AD, brain tumors: diencephalic or midbrain), *psychiatric illness* (psychoses, anxiety/panic disorders, bipolar disorder: these may cause nocturnal insomnia with subsequent EDS), *circadian rhythm disturbances*, and *idiopathic hypersomnia* (excessive sleepiness associated with normal or prolonged non-REM sleep episodes: sleep is unrefreshing despite duration and cataplexy not expected).

Differentials for hypnagogic hallucinations include *psychoses* and *lesions of temporo-occipital cortex* (tumor, stroke, hemorrhage, abscess, etc). Differentials for cataplexy include *drop attacks, syncope* (*see* pp. 167, 176–179), and seizures (atonic, complex partial, or absence). Sleep paralysis may occur as an *isolated and physiological response*, as part of familial sleep paralysis or could be mistaken for an *upper brainstem stroke* ("top of the basilar syndrome" secondary to basilar artery thrombosis: transient symptoms unexpected) or *hyperkalemic* or *hypokalemic periodic paralysis* (Na^+ and Ca^{2+} channelopathies respectively; associated with changes in serum K^+).

Investigations

The diagnostic tests of choice include overnight polysomnography and multiple sleep latency test. Polysomnography may show short sleep latency, excessive sleep disruption with frequent arousals, reduced total sleep time, reduced slow-wave sleep, and sleep-onset REM. Multiple sleep latency test may show a mean sleep latency of less than 8 minutes, or more than two sleep-onset REM (out of four to five recordings), or both. In equivocal cases, neuroimaging (CT/MRI of the brain), EEG, electrodiagnostic tests, pulmonary function tests, cardiological evaluation, and serum/urine toxicology may be required to exclude other etiologies.

Management

The mainstay of treatment for narcolepsy is pharmacological. Treatments can be divided into drugs to control EDS (sleep attacks) and drugs to control cataplexy and the other manifestations of the disorder. EDS may be controlled with amphetamines such as methylphenidate, pemoline, dextroamphetamine, adderall, or modafinil (side effects include headache, nervousness, with or without nausea). The treatment of cataplexy and the other manifestations of

narcolepsy include TCAs (e.g., imipramine, clomipramine) and SSRIs (e.g., fluoxetine, paroxetine). Nonpharmacological measures include general improvement in sleep hygiene and short, scheduled daytime naps. Lifestyle and job modifications may be necessary to ensure a safe environment. Involvement in a narcolepsy support group and regular exercise could also be useful.

Prognosis

Narcolepsy is a chronic, nonprogressive lifelong disease. Its natural history is poorly defined, but patients with narcolepsy have worse functional ratings and higher disability scores than age-matched controls with time. Narcoleptics may also develop OSA, periodic leg movements of sleep (PLMS), or RBD that require additional treatment. Pharmacological treatment for narcolepsy may result in more than 70–80% improvement in symptoms, with approximately 50–60% of patients reporting significant symptomatic relief. Prognosis is also influenced by the risk of chronically taking these medications.

Counseling

Patients should be aware that narcolepsy is a lifelong disease that can be debilitating. Pharmacological options should be discussed with the patient and a risk–benefit analysis needs to be performed individually. Patients with narcolepsy may develop anxiety, depression, sexual dysfunction, morning headaches, or memory dysfunction, so patients should be counseled to seek medical intervention if these arise. Driving and operating heavy machinery should be avoided and involvement in a narcolepsy support group may help with coping with the disease.

SUMMARY

- **Narcolepsy** is a **REM-sleep disorder** associated with dysfunction of **orexin (hypocretin)**-secreting cells in the **hypothalamus**.
- The classic tetrad consists of **EDS** (sleep attacks), **hypnagogic hallucinations**, **cataplexy**, and **sleep paralysis**.
- Differential considerations for EDS: **OSA**, **sleep deprivation**, **drug-induced hypersomnolence**, **medical causes**, **neurological causes**, **psychiatric illness**, **circadian rhythm disturbances**, and **idiopathic hypersomnia**.
- Differential considerations for hypnagogic hallucinations include **psychoses** and **lesions of temporo-occipital cortex**, for cataplexy include **drop attacks**, **syncope**, and **seizures** and for sleep paralysis include **normal** physiological response, **familial sleep paralysis**, **upper brainstem stroke**, or **periodic paralysis**.

- Diagnostic tests of choice are **overnight polysomnography** and **multiple sleep latency test**.
- Pharmacological treatments include **amphetamines** and **modafinil** for EDS, **TCAs** and **SSRIs** for cataplexy and other symptoms.
- Nonpharmacological treatments include **general improvement in sleep hygiene**, **short**, **scheduled daytime naps**, **lifestyle** and **job modifications**, involvement in a **narcolepsy support group**, and **regular exercise**.
- **Long-term disability** expected with chronic narcolepsy.
- **Risk–benefit ratio** needs to be considered in narcoleptics on long-term pharmacotherapy.

CASE 2

A 67-year-old man came to the clinic with his wife. She was concerned that over the past 4 months, he had been having "violent dreams" resulting in aggressive behavior in bed. During the past week, she had been struck several times on the face and chest and he had kicked the bedside lamp over. He denied any recollection of any of these events. Neurological examination was normal.

Localization

Aggressive violent behavior may indicate dysfunction of the limbic cortex (bilateral mesial frontal and temporal lobes, especially the amygdala). Aggressive behavior may also occur with global cerebral dysfunction (delirium or dementia) without any particular localizing features. The occurrence of these episodes during sleep may also implicate dysfunction in sleep-modulating centers in the hypothalamus, thalamus, or brainstem (midbrain and pons). In summary, the clinical presentation is nonlocalizing, with possible involvement of the bilateral cerebral cortex, diencephalon, and brainstem.

Differential Diagnosis

The most likely diagnosis for violent aggressive behavior during REM sleep in an elderly main is *REM sleep behavior disorder* (RBD). This is an idiopathic disorder in 50–60% of patients. In the remainder, causal associations that have been described include *neurodegenerative disorders* (e.g., PD, MSA, DLBD, CBGD, PSP), *sleep disorders* (e.g., narcolepsy), *toxins* (e.g., alcohol), *drugs* (e.g., sedative-hypnotics, TCAs, anticholinergics), or *thalamic/brainstem lesions*. Differentials include *nocturnal complex partial seizures* (temporal or frontal foci), *psychiatric disorders* (e.g., pain attack, psychosis), *delirium* (*see* pp. 94–96), or *sleep disorders* (e.g., night terrors, nightmares, sleep walking, confusional arousals).

Investigations

The diagnostic test of choice for RBD is nocturnal polysomnography. This shows REM sleep without muscle hypotonia/atonia. In atypical cases, standard 16-channel EEG may be performed to exclude complex partial seizures. Laboratory investigations may include serum/urine toxicology screens if there is a history of drug/toxin exposure. MRI brain may be useful in establishing secondary causes for RBD if suggested by the clinical evaluation.

Management

Any underlying conditions should be identified and appropriately treated if possible. Pharmacological treatment for RBD consists of low-dose medium- to long-acting benzodiazepines, such as clonazepam. There is an approximately 90% response rate to this medication that occurs early in the treatment course. Patients may need to sleep alone with the removal of any potentially dangerous objects in proximity to the bed until symptoms are controlled. Supportive care and reassurance should be offered to bed partners.

Prognosis

RBD is a life-long, chronic sleep disorder that is usually adequately controlled with benzodiazepines. Cessation of medication usually results in symptom recurrence. Prognosis would also be modified by any underlying secondary causes.

Counseling

Patients should be aware of the excellent response to benzodiazepines and the risks and benefit of chronic use should be discussed fully. Bed partners should be provided with reassurance and emotional support. Alcohol and other drugs that may induce RBD should be avoided.

SUMMARY

- **RBD** usually presents with **aggressive behavior** during **REM sleep** and is more common in **elderly men**.
- Etiologies include **idiopathic** (50–60%), **neurodegenerative disorders**, **sleep disorders**, **toxins**, **drugs**, or **thalamic/brainstem lesions**.
- Differentials include **nocturnal complex partial seizures**, **psychiatric disorders**, **delirium**, or **sleep disorders** such as night terrors, nightmares, sleep walking, and confusional arousals.
- **Absence of REM sleep hypotonia/atonia** on **nocturnal polysomnography** establishes the diagnosis. Secondary causes should be evaluated for if clinically indicated.
- Treatment of choice is **medium- to long-acting benzodiazepines** (e.g., **clonazepam**), with **approximately 90%** response rate.

- **Supportive care**, **emotional support**, and **injury precautions** are necessary adjuncts to pharmacotherapy.
- **Cessation of drug therapy** results in **symptom recurrence**.
- RBD is a **chronic disorder** and prognosis may be modified by identifiable underlying causes.

CASE 3

A 48-year-old woman complained of progressively worsening urge to move her legs while lying down in bed for about 3 months, especially before falling asleep. She experienced a creepy, unpleasant sensation in her legs before the urge to move. These symptoms were readily relieved by walking around her bedroom but returned once she got back into bed. Her spouse had also noticed intermittent repetitive stereotypical lower extremity movements when she was asleep. Dramatization showed that she flexes her hip and knee, dorsiflexes the ankle, and extends the great toe. Neurological examination was normal.

Localization

Abnormal sensory perception in the lower extremities may be secondary to peripheral nerve dysfunction (sensory nerves, lumbosacral plexi, lumbar and sacral nerve roots, or dorsal root ganglia) or central dysfunction (e.g., lumbar and sacral spinal cord, periaqueductal gray of the midbrain, thalamus). Abnormal stereotypical motor activity may suggest hyperexcitation of the frontal cortex or lack of cortical inhibition of brainstem (e.g., red nucleus in midbrain, vestibular nucleus at the pontomedullary junction) and spinal cord AHC that influence motor activity. The normal examination does not provide any further localizing clues. In summary, the underlying process most likely affects central or peripheral sensorimotor pathways or both.

Differential Diagnosis

The most likely diagnosis for a non-REM sleep disorder characterized by irresistible urges to move the legs in association with creeping sensations that is relieved by walking, and associated with *periodic leg movements of sleep* (PLMS) is *restless legs syndrome* (RLS). RLS is a complex sensorimotor sleep disorder of unknown etiology that predominantly affects the legs. PLMS may occur in approximately 80% of patients with RLS.

In a few patients, RLS is caused by *neurological disorders*: *central causes* include MS, hyperexplexia, PD, myelopathy; *peripheral causes* include poliomyelitis, lumbosacral radiculopathy, polyneuropathy, Isaac's syndrome (neuromyotonia) or *mixed* (ALS); *medical causes* include iron-deficiency anemia, uremia, DM, hypothyroidism, peripheral vascular disease, and cancer;

drug etiologies include as Ca^{2+} channel antagonists, antiemetics, lithium, TCAs, SSRIs, alcohol, caffeine, sedative-hypnotic drug withdrawal; or *pregnancy*.

Differentials include *akathisia* (motor restlessness commonly associated with neuroleptics, present mostly during the day with an inability to stand or sit still), *myokymia* (undulating muscle movements associated with nerve demyelination), *painful nocturnal leg cramps*, *essential myoclonus* (benign myoclonic jerks of unknown etiology), *hypnic jerks* (sudden brief myoclonic jerks of limbs or entire body lasting for a few seconds at sleep onset and triggered by stress, fatigue, or sleep deprivation), *cramp-fasciculation syndrome* (a syndrome of peripheral nerve hyperexcitability), *complex regional pain syndrome,* and *anxiety/depression*.

Investigations

RLS is a clinical diagnosis, so a detailed clinical history is paramount. If PLMS is suggested clinically, overnight polysomnography should be performed. Sleep disturbance (with arousals) and more than five PLMS per hour of sleep is diagnostic of PLMS. Secondary causes for RLS should be investigated for. Laboratory tests may include CBC with differential, electrolytes, iron studies including ferritin and transferrin, vitamin B_{12} levels, folate, fasting glucose or oral glucose tolerance test, TFT and serum/urine toxicology. EMG/NCS should be performed to exclude lower motor neuron and peripheral sensory causes for RLS, as well as to exclude conditions that resemble idiopathic RLS.

Management

In general, any underlying conditions or exacerbating factors should be eliminated in treating secondary RLS. Drugs should be started at the lowest therapeutic dose and slowly increased to maximum effect. Pharmacological treatment includes *dopaminergic agents* such as *carbidopa/levodopa* (ADRs: nausea/vomiting, headache), pergolide (ADRs: hypotension, nasal stuffiness), *pramipexole* and *ropinirole* (ADRs: nausea, sleepiness, peripheral edema); *AEDs* such as *gabapentin* (ADRs: somnolence, ataxia, fatigue at higher doses), *carbamazepine* (ADRs: ataxia, hepatic dysfunction, hyponatremia); *benzodiazepines* such as *clonazepam, temazepam* (ADRs: daytime somnolence, confusion, respiratory and cardiac depression at high doses, tolerance/dependence); *opioids* such as codeine, oxycodone, tramadol, methadone (ADRs: constipation, urinary retention, tolerance/dependence); *adrenergic agents* such as *propranolol* (β-blocker) or the central α_2 agonist, *clonidine*, and *baclofen*. In mild cases of RLS-PLMS, one may start with gabapentin, whereas moderate to severe cases may be treated with dopamine agonists pramipexole or ropinirole initially. Polypharmacy may be required in refractory cases.

Prognosis

RLS is not a life-threatening disorder, but if untreated, may cause significant reduction in the quality of life and functional capabilities of patients. There is an approximately 80% good response rate to drug therapy in RLS at a mean follow-up of 16 months. Outcomes may be better in patients with RLS without PLMS. For secondary RLS, prognosis would also be modified by the underlying cause.

Counseling

RLS is a relatively common sleep disorder, affecting about 5–20% of the general population. Patients and their bed partners should be reassured that the condition is not life-threatening. Pharmacotherapy should be offered to patients with symptoms significant enough to affect their quality of life and functional status. They should be aware of the potentially good response rates, as well as the adverse effects of these drugs. Secondary causes should be treated meticulously and specialist help may be required for medical causes of RLS.

SUMMARY

- **RLS** is a **non-REM sleep disorder** characterized by **irresistible urges** to move the **legs** in association with **creeping sensations** that are relieved by **walking**.
- **PLMS** occur in about **80%** of RLS patients.
- Causes include **idiopathic** and **secondary** etiologies such as **neurological disorders**, **medical disease**, **drugs/toxins**, and **pregnancy**.
- Differentials include **akathisia**, **myokymia**, **painful nocturnal leg cramps**, **essential myoclonus**, **hypnic jerks**, **cramp-fasciculation syndrome**, **complex regional pain syndrome**, or **anxiety/depression**.
- Diagnosis is established **clinically**. If PLMS is suggested, nocturnal polysomnography showing **more than five PLMS per hour of sleep with arousals** is diagnostic.
- Treat any **underlying conditions** and remove **exacerbating** or **causative** agents.
- Pharmacotherapy of RLS includes **dopamine agonists**, **AEDs**, **benzodiazepines**, **opioids**, **adrenergic agents**, and **baclofen**.
- **Approximately 80%** of patients demonstrate good responses after mean follow-up of **16 months**. Better outcomes may occur if **PLMS is absent**.
- RLS-PLMS is not a life-threatening disease, but may significantly **reduce quality of life** and **functional capabilities** if untreated. Prognosis may be modified by underlying causes.
- Patients should be aware of prognostic data and **reassurance** should be provided to patients and their bed partners.

CASE 4

A 57-year-old overweight man complained of excessive daytime fatigue, forgetfulness, and increased irritability for about 6 months. He stated that he frequently woke up at night with choking spells, resulting in poor sleep. His wife said that he has had spells of breathing cessation during sleep that concern her. Clinical examination was nonrevealing.

Localization

Forgetfulness and irritability could localize to the bilateral temporal or frontal lobes. EDS implies poor nocturnal sleep (insomnia), and is nonlocalizing. Choking and intermittent apneic spells could indicate upper airway obstruction or dysfunction of respiratory centers in the medulla. In summary, the underlying process localizes diffusely to the cerebral cortex, with brainstem involvement or airway disease.

Differential Diagnosis

The most likely diagnosis for a chronic sleep disorder characterized by EDS with poor nocturnal sleep associated with choking and apneic spells in an overweight man is *obstructive sleep apnea-hypopnea syndrome* (OSAHS). This is a syndrome that occurs mainly in men over the age of 40 (~85% of cases) or postmenopausal women and associated with obesity in approximately 70% of patients. Other causes of sleep apnea include *central* (dysfunction of medullary respiratory centers causing cessation of airflow without respiratory effort) or *mixed* (central and upper airway obstruction) etiologies. In some patients, OSAHS is associated with hypertension, cardiac arrhythmias, or CHF.

Differentials for sleep-disordered breathing include *upper airway resistance syndrome* (subtle airflow limitations due to resistance of airways, resulting in frequent nocturnal arousals without apnea/hypopnea), *Cheyne-Stokes breathing* (central apnea interspersed between crescendo–decrescendo respiratory sequence in a cyclical pattern), *dysrhythmic/ataxic breathing* (nonrhythmic respiratory pattern with irregular amplitude and rhythm, associated with brainstem dysfunction), *apneustic breathing* (prolonged inspiratory phase associated with pontine lesions), and *alveolar hypoventilation* (associated with neuromuscular disorders such as MG, GBS, or myotonic dystrophy causing a restrictive lung deficit).

Investigations

Nocturnal polysomnography should be performed to establish the diagnosis of OSAHS. Findings include apnea-hypopnea index (AHI: number of apneic or hypopneic episodes per hour of sleep) >5 (mild: 5–19, moderate: 20–49 and severe: >50), arousal index (AI) >15 (10–15: borderline, <10: normal), reduced oxygen saturations (<90%), and reduced stage III, IV non-REM and REM

sleep. Other causes of sleep-disordered breathing can be deduced with polysomnography. Pulmonary function tests should be considered to exclude intrinsic bronchopulmonary disease in OSAHS or restrictive respiratory deficits as seen in neuromuscular disorders. Cardiac evaluation (such as EKG, Holter monitor, telemetry, or echocardiogram) may be required if there is clinical evidence of heart disease.

Management

Therapy for OSAHS can be divided into general or direct modalities. General measures include weight reduction, treating any associated diseases, and avoidance of alcohol or sedative-hypnotics. Direct therapy can be divided into pharmacological, mechanical, and surgical options. Medications have very limited role in treating OSAHS; partial success in mild OSAHS has been described with protriptyline. Mild central apnea syndrome may respond to acetazolamide at high altitudes.

Mechanical devices include nasal continuous positive airway pressure (CPAP; option of choice), bivalve positive airway pressure (BiPAP), and dental and tongue-retaining devices. Surgical therapy should be considered for severe cases refractory to nasal CPAP: uvulopalatopharyngoplasty (UPPP: ~50% of patients significantly improve but many still require CPAP for residual apneas), tonsillectomy, adenoidectomy, maxillofacial reconstructions, or in rare cases, tracheostomy. Diaphragmatic pacing or electrophrenic respiration may be used in patients with central apnea syndrome.

Prognosis

Data on the natural history of OSAHS is limited by the lack of prospective studies. OSAHS may be a progressive disorder with worsening apneic/hypopneic spells if left untreated. Poor quality of life usually results in patients seeking medical attention. Morbidities associated with OSAHS include hypertension, cardiac arrhythmias, angina, MI, and stroke. These medical complications may occur in about 20–45% of patients over a mean follow-up of 17 months. Mortality is increased in comparison to matched controls and is associated with the increased risk of cardiovascular disease. Treatment (nasal CPAP, UPPP) has been shown to improve outcomes in moderate to severe cases (AHI >35) in comparison with patients who refused therapy.

Counseling

Patients should be aware of the prognostic data and potential benefit of treatment. Compliance with CPAP/BiPAP should be encouraged and measures should be undertaken to maximize patient comfort (such as humidified air, mask modifications). Complications should be aggressively treated and specialist cardiological consultation should be sought. Weight reduction and cessation of alcohol and sedative use should be advised.

SUMMARY

- **OSAHS** is a **chronic**, **progressive** sleep disorder most common in **obese men over the age of 40**.
- Etiologies for sleep apnea include **upper airway obstruction**, **central (medullary)** or **mixed (both)**.
- Differentials for sleep-disordered breathing include **upper airway resistance syndrome**, **Cheyne-Stokes**, **dysrhythmic/ataxic** or **apneustic breathing**, or **alveolar hypoventilation**.
- Diagnostic test for OSAHS is **nocturnal polysomnography**. **AHI >5**, **AI >15**, **reduced oxygen saturations (<90%)** and **reduced stage III**, **IV non-REM and REM sleep** are diagnostic variables.
- Treatment includes **general measures** and **direct therapy**. Direct therapy includes **medications** (limited use, in mild cases only), **mechanical** (especially CPAP), and **surgical** (especially UPPP) options.
- Complications of OSAHS are **cardiac**, **neurological**, and **social**.
- Mortality is **increased** in OSAHS secondary to **cardiovascular disease** and treatment has been shown to improve outcomes.